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10/748,897	12/29/2003	Anthony Joonkyoo Yun	PALO-002	7432

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,897	YUN ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,11-55 and 57-68* is/are pending in the application.

4a) Of the above claim(s) *29-40,42-55 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 11-28, 41, 62-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 12/4/2008. Claims 1, 5-10, 56, 58-61 have been cancelled. Claim 1 has been amended, claims 29-40, 42-55 have been withdrawn and claims 6-68 have been added new. Claims 1, 3, 4, 11-55, 57-68 are pending and claims 1, 3, 4, 11-28, 41, 57, 62-68 are examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the 112(1) rejections, rejection of claims 1, 63 under 35 U.S.C. 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003). Claims 1, 16, 18 under 35 U.S.C. 103(a) as being unpatentable over Guilli et al. (Cardiovascular Research, 2001, 208-216) in view of Bugiardini et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90), claims 1, 26-27 under 35 U.S.C. 103(a) as being unpatentable over Hill et al. (U.S. 6,449,507) and Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003), Claims 1, 11, 13 and 24 under 35 U.S.C. 103(a) as being unpatentable over Garrett et al. (Quarterly J of Expt. Physiology, 1987, 72, 357-68) have been fully considered and found not to be persuasive. The 102 rejections are withdrawn due to the amendment of the claim 1. Applicants' amendments and addition of new claims necessitated the new and modified rejections presented in this action. Accordingly, the action is made Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 11-28, 41, 62-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. The specification does not teach administration of a beta-blocker to a subject to treat such subjects for at least one of the conditions listed in claim 1. The specification also does not provide support of modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. The specification does not provide adequate description and there are no specific examples to provide support to the claims. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not provide support to the subject matter of administration of a beta blocker to a subject to treat said subject for at least one of the conditions listed in claim 1 wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and, (8) the quantity of experimentation necessary.

Claims 1, 3, 4, 11-28, 41, 62-68 are rejected under 35 U.S.C. 112, first paragraph, because the prior art, while being enabling for a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating comprising administering an effective amount of at least one beta blocker to conditions like asthma, hypertension, glaucoma, migraine, anxiety disorders does not reasonably provide enablement for treating all the diseases or disorders listed in claim 1 with all the beta blockers and in combination with all non-beta blocking agents listed in claim 24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(1, 5) The nature of the invention and the breadth of the claims:

The instant claims are directed to a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a

portion of said subject's autonomic nervous system by administering an effective amount of at least one beta-blocker to said subject to treat said subject for at least one of: neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2 dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions; chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma. Claim 21 is limited to few beta blockers, claim 41 to few aging associated conditions. Claims 1, 3, 4, 11-20, 22-28, 62, 63 are very broad with respect to the conditions, number of beta blockers and number of non-beta blocking agents (listed in claim 24).

(3) The relative skill of those in the art:

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

(4) The predictability of the art:

Despite the advance training of those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a

compound based on the structure alone. It is also not possible to predict the efficacy of a given class of compounds for the treatment of a particular disease absent a mechanistic link between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a patient or in a model that has been established as being predictive of treatment efficacy. In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Absent experimental tests verifying the efficacy of a compound or a strong nexus between the known pharmacological activity of a class of agents and the etiology and/or pathophysiology of the condition, it is impossible to predict whether the compound or class of compounds (here beta blockers) would actually be effective for treating every single condition listed in clam 1. It is impossible to predict that every single beta blocker can be used in combination with every single non-beta blocker class of compounds listed in claim 24. It is impossible to predict that every single beta blocker used in a method of treatment of condition caused by an autonomic nervous system abnormality will be effective in the treatment of every single disorder or disease in the different classes of disorders (that are etiologically different) listed in claim 1. Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non beta blockers claimed in claim 24 of the instant

application) along with propranolol or atelenol or alprenolol (p 1584, para 2). Hence it is highly unpredictable what the outcome would be to due to the interaction of beta blockers with other drugs. Hence there is high unpredictability in the treatment of abnormal autonomic nervous disorders comprising administering a beta blocker with a non beta blocking agent. Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). There is a high degree of unpredictability involved in a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta-blocker to said subject for all the diseases and disorders listed.

(2) The state of the prior art:

Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non beta blockers claimed in claim 24 of the instant application) along with propranolol or atelenol or alprenolol (p 1584, para 2). Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). Houston (Cardiol Clin, 1986, Feb 4(1), 117-35) teaches that several antihypertensive drugs have an adverse effect on glucose tolerance that may partially or completely negate the beneficial effects of reducing blood pressure as it relates to the incidence of coronary heart disease and its complications and beta-blockers without intrinsic sympathomimetic

activity have the greatest adverse effect on glucose intolerance. Liebermann et al. (Br J Obstet Gynaecol, 1978, 678-83, abstract) teaches that beta-adrenergic blockade is harmful to the hypoxic fetus, for these reasons the use of propranolol in hypertensive pregnancies complicated by placental insufficiency may be contraindicated unless there is no satisfactory alternative (See Abstract). Allen et al. teaches that there was an adverse effect of practolol, the occurrence of sinus bradycardia with or without an increase in the frequency of ventricular ectopic beats (See abstract). It has been well known in the prior art that beta blockers are useful in the treatment of angina, heart failure, high blood pressure, glaucoma and various disorders (http://en.wikipedia.org/wiki/Beta_blocker). Salpeter et al. (Cochrane Database of Systemic Reviews, 4, 2002) teach that beta blocker therapy has mortality benefits in patients with hypertension, heart failure, coronary artery disease as well as during the postoperative period (see Abstract). In summary, the guidance from prior art is for the use of beta blockers in conditions like hypertension, heart failure, coronary artery disease as well as during the postoperative period, glaucoma etc, the adverse effects of certain beta blockers and the contraindications of beta blockers in combination with calcium channel blockers. The prior art or the specification does not teach that every single disease or disorder in the different classes of disorders (that are etiologically different) listed in claim 1 will be effectively treated by administration of the beta blockers (known and yet to be discovered) nor does the prior art or specification teach that every combination of beta blocker with a non-beta blocking agent can be used without interactions and be effective in the treatment.

(6, 7) The amount of guidance presented and the presence of working examples:

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. The specification does not teach administration of a beta-blocker to a subject to treat such subjects for at least one of the conditions listed in claim 1. The specification also does not provide support of modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. There is no guidance in the specification with respect to the treatment of conditions with high parasympathetic activity with normal sympathetic activity. The specification does not provide specific examples to provide support to the claims. Also, there is a high degree of unpredictability involved in combining a beta blocker with a non-beta blocking drug as there may be drug interactions and if there are any adverse effects such combination may not be workable. In summary, Applicant has provided little guidance beyond what was recognized in the art at the time of filing.

(8) The quantity of experimentation needed:

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. With Applicants'

guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct these experiments administering beta blockers for every single condition listed in claim 1 and with combination of non-beta blockers listed in claim 24. Considering the unpredictability of the combination of compounds due to their drug interactions, this would be an arduous and daunting task. It would require undue experimentation to test each beta blocker for all the conditions listed in a method of modulating the autonomic nervous system and treating the subjects for those conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. It would require undue experimentation to test each beta blocker with every single non beta blocking agent listed in claim 24 for every condition listed in a method of modulating the autonomic nervous system and treating the subjects for those conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. It would require undue experimentation to test all beta blockers for every condition listed in a method of modulating the autonomic nervous system and treating the subjects for those conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective

amount of at least one beta-blocker to said subject to treat said subject for at least one of the conditions listed in claim 1. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003) in view of Rang et al. (Applicant cited reference: Rang et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Duke University, 2000) and further in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Lampert et al. teaches propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients (see Abstract, p 140, Discussion, para 1). Thus from the teachings of Gambardella et al. and Lampert et al. it is evident that parasympathetic activity is increased after propranolol administration with heart conditions. Lampert et al. teach administration of 180 or 240 mg/day of propranolol (See Methods).

It would have been obvious to one of ordinary skill in the art at the time of the invention that administration of a beta blocker such as propranolol increases the parasympathetic activity because of the teachings of Lampert et al. Lampert et al. teach that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients. Hence by administration of same drug (as claimed), propranolol to patients would obviously have the same pharmacological effects such as increase in parasympathetic activity. The reference does not explicitly teach that the modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. However, Lampert et al. teach administration of propranolol 180 or 240 mg/day. The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Lampert et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed, in the dosage amount recommended in the specification of the instant application.

The reference does not teach that the method further comprises of determining the sympathetic and parasympathetic functions are substantially equal.

Rang as cited by Applicants' in the specification teaches non invasive procedure to assess the autonomic cardiovascular control in patients with hypertensive disorder (See abstract).

Autonomic dysfunction document teaches various methods to measure the autonomic functions by analyzing heart rate, blood pressure variability etc.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the equality in sympathetic and parasympathetic functions by using the methods taught by Rang and Autonomic dysfunction document. One having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal because evaluation or assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation etc..

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time

of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals.

Claims 1, 16, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guilli et al. (Cardiovascular Research, 2001, 208-216) in view of Bugiardini et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90) in view of Rang et al. (Applicant cited reference: Rang et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Duke University, 2000) and further in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (see Abstract).

The reference does not teach administration of a beta blocker in a method of treating a subject to a condition caused by an autonomic nervous system.

Bugiardini et al. teach administration of propranolol to patients with X syndrome and further teach that the average number of ischemic episodes per 24 hours was significantly reduced during propranolol therapy compared with placebo (see abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered a beta blocker such as propranolol in a method of treating a subject to a condition caused by an autonomic nervous system where the abnormality comprises abnormally low parasympathetic activity but normal sympathetic activity such as syndrome X because of the teachings of Bugiardini et al. One having ordinary skill in the art would have been motivated to administer a beta blocker such as propranolol in expectation of reducing the ischemic episodes in patients with syndrome X. The references do not explicitly teach that the modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. However, Bugiardini et al. teach administration of propranolol 120 to 160 mg daily (see abstract). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Bugiardini et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed, in the dosage amount recommended in the specification of the instant application.

The reference does not teach that the method further comprises of determining the sympathetic and parasympathetic functions are substantially equal.

Rang as cited by Applicants' in the specification teaches non invasive procedure to assess the autonomic cardiovascular control in patients with hypertensive disorder (See abstract).

Autonomic dysfunction document teaches various methods to measure the autonomic functions by analyzing heart rate, blood pressure variability etc.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the equality in sympathetic and parasympathetic functions by using the methods taught by Rang and Autonomic dysfunction document. One having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal because evaluation or assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation etc.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment

therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals.

Claims 1, 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hill et al. (U.S. 6,449,507) and Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003) in view of Rang et al. (Applicant cited reference: Rang et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Duke University, 2000) and further in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Hill et al. teach the stimulation of nerve or nerve fibers (vagus nerve fibers, hypoglossal nerve fibers, phrenic nerve fibers, parasympathetic nerve fibers, and sympathetic nerve fibers, a vagal nerve) by using electrodes and electrical current and further comprising beta-blockers such as propranolol in a medical procedure such as beating heart surgery, arrythmias, vascular surgery, neurosurgery etc which are aging

associated conditions (col. 2, lines 61-65, col. 17, claim 1, claim 10, col. 18, claim 19, co. 20, claim 50). The reference teaches that drugs, drug formulations or compositions suitable for administration to a patient during a medical procedure may include a pharmaceutically acceptable carrier or solution in an appropriate dosage (col. 9, lines 55-59).

Lampert et al.'s teachings discussed as above. Lampert et al. teach that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer a beta blocker such as propranolol to stimulate a portion of autonomic nervous system because of the teachings of Hill et al. One having ordinary skill in the art at the time of the invention would have been motivated in expectation of success from Hill's teachings. The reference does not explicitly teach that the modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Lampert et al. teach administration of propranolol 180 or 240 mg/day. The specification of the instant invention recommends administration of propranolol of about 80 mg to about 320 mg a day taken in, two, three, or four divided doses (para 0091). Hence Lampert et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with

abnormality in autonomic nervous system as claimed, in the dosage amount recommended in the specification of the instant application.

The reference does not teach that the method further comprises of determining the sympathetic and parasympathetic functions are substantially equal.

Rang as cited by Applicants' in the specification teaches non invasive procedure to assess the autonomic cardiovascular control in patients with hypertensive disorder (See abstract).

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It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the equality in sympathetic and parasympathetic functions by using the methods taught by Rang and Autonomic dysfunction document. One having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal because evaluation or assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation etc.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals.

Claims 1, 11, 13 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garrett et al. (Quarterly J of Expt. Physiology, 1987, 72, 357-68) in view of Rang et al. (Applicant cited reference: Rang et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Duke University, 2000) and further in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Garrett et al. teach administration of a beta blocker such as propranolol 1mg/kg (calculates to 70 mg for a 70 kg patient) to modulate autonomic nervous system in salivary glands. The reference teaches that parasympathetic and sympathetic systems can be stimulated by administration of a beta blocker such as propranolol. The reference teaches high parasympathetic stimulation and partial and complete inhibition of secretion of kallikrein by administration of propranolol followed by hydroergotamine (an alpha blocker). The reference teaches the modulation of parasympathetic and sympathetic activities and thus teaches the high parasympathetic and normal sympathetic condition at one stage of modulation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer a beta blocker such as propranolol in a method of treating a subject to a condition caused by an abnormality of autonomic nervous system wherein the abnormality comprises high parasympathetic activity and normal sympathetic activity from Garett et al.'s teachings. The reference teaches that parasympathetic and sympathetic systems can be stimulated by administration of a beta blocker such as propranolol. The reference further teaches the inhibition of secretion of kallikrein by administration of propranolol followed by hydroergotamine (an alpha blocker). Hence by modulating the autonomic nervous system Garrett et al. teaches the system with a high parasympathetic activity and a normal sympathetic activity.

The reference does not teach that the method further comprises of determining the sympathetic and parasympathetic functions are substantially equal.

Rang as cited by Applicants' in the specification teaches non invasive procedure to assess the autonomic cardiovascular control in patients with hypertensive disorder (See abstract).

Autonomic dysfunction document teaches various methods to measure the autonomic functions by analyzing heart rate, blood pressure variability etc.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the equality in sympathetic and parasympathetic functions by using the methods taught by Rang and Autonomic dysfunction document. One having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal because evaluation or assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation etc.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment

therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals.

Claims 1, 3, 4, 14, 19-22, 28, 41, 62-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297) in view of Rang et al. (Applicant cited reference: Rang et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Duke University, 2000) and further in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Gambardella et al. teach a method of treating a condition due to deficient parasympathetic activity associated with elevated basal metabolic rate in cancer patients by oral administration of propranolol (see Abstract, p 295, para 1, lines 1-8, p 296, para 4, 1-5). The reference teaches the autonomic nervous system dysfunction in cancer patients with elevated basal metabolic rate, there is an unbalanced sympathetic

(SNS)/parasympathetic nervous system (PNS) ratio which may exist due to SNS overactivity in cancer patients due to impaired PNS activity. The reference further teaches that beta-blocker such as propranolol administration may be useful to counteract the negative impact of the SNS on metabolic pathways (p 297, para 3 continued on 298). Hence the reference teaches the sympathetic bias in at least a portion of autonomic nervous system, abnormality characterized by sympathetic bias, parasympathetic bias with an unbalanced SNS/PNS ratio with high SNS activity and low PNS activity. The reference does not explicitly teach that modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Gambardella et al. teach administration of propranolol 40 mg twice daily (80 mg total) (see Abstract). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Gambardella et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to same set of patients with abnormality in autonomic nervous system as claimed in the dosage amount recommended in the specification of the instant application.

The reference does not teach that the method further comprises of determining the sympathetic and parasympathetic functions are substantially equal.

Rang as cited by Applicants' in the specification teaches non invasive procedure to assess the autonomic cardiovascular control in patients with hypertensive disorder (See abstract).

Autonomic dysfunction document teaches various methods to measure the autonomic functions by analyzing heart rate, blood pressure variability etc.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the equality in sympathetic and parasympathetic functions by using the methods taught by Rang and Autonomic dysfunction document. One having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal because evaluation or assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation as dysfunctions of the autonomic nervous systems encompass various and multiple disorders.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop

in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals.

Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, 62-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brevetti et al. (Brief communications, Nov 1981, p 938-941) in view of Rang et al. (Applicant cited reference: Rang et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Duke University, 2000) and further in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Brevetti et al. teach an intravenous and oral administration of propranolol for the treatment of Shy-Drager syndrome, a severe degeneration of the autonomic nervous system. The reference further teaches that orthostatic hypotension a condition of Shy-Drager syndrome is mainly dependent on peripheral vasodilation without the normal

response of postural vasoconstriction and may be a consequence of an imbalance of alpha and beta adrenoreceptor activity in peripheral nervous system and that beta-blockade may provide an effective means of treating orthostatic hypotension in patients with Shy-Drager syndrome (p 940 para 2, lines 1-5, continued on page 941). The reference teaches a sympathetic bias and a parasympathetic bias in at least a portion of said autonomic nervous system. The reference does not explicitly teach that modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Brevetti et al. teach administration of propranolol 40 mg three times daily (120 mg total) (p 939, para 1, lines 7-8). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Brevetti et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to same subjects with abnormality in autonomic nervous system as claimed in the dosage amount recommended in the specification of the instant application.

The reference does not teach that the method further comprises of determining the sympathetic and parasympathetic functions are substantially equal.

Rang as cited by Applicants' in the specification teaches non invasive procedure to assess the autonomic cardiovascular control in patients with hypertensive disorder (See abstract).

Autonomic dysfunction document teaches various methods to measure the autonomic functions by analyzing heart rate, blood pressure variability etc.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the equality in sympathetic and parasympathetic functions by using the methods taught by Rang and Autonomic dysfunction document. One having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal because evaluation or assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation etc.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time

of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals.

Claims 1, 21, 23-25, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al. (The J of Intl Med Research, 1988, 16, 173-181) in view of Rang et al. (Applicant cited reference: Rang et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Duke University, 2000) and further in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Davies et al. teach the administration of ibuprofen, a non-steroidal anti-inflammatory drug along with an anti-hypertensive agent and a beta-blocker such as propranolol (see Abstract) to group of patients with hypertension. It is inherent that hypertension, an age-associated condition is common in elderly patients and parasympathetic nerves influence cerebral blood flow during hypertension. The reference does not explicitly teach that modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Davies et al teaches administration of propranolol 40-

240 mg/day (p 176, Propranolol treatment group). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Davies et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to same subjects with abnormality in autonomic nervous system as claimed in the dosage amount recommended in the specification of the instant application.

The reference does not teach that the method further comprises of determining the sympathetic and parasympathetic functions are substantially equal.

Rang as cited by Applicants' in the specification teaches non invasive procedure to assess the autonomic cardiovascular control in patients with hypertensive disorder (See abstract).

Autonomic dysfunction document teaches various methods to measure the autonomic functions by analyzing heart rate, blood pressure variability etc.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the equality in sympathetic and parasympathetic functions by using the methods taught by Rang and Autonomic dysfunction document. One having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal because evaluation or assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation etc.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals.

Claims 1 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Broder et al. (U.S. 6,284,800) in view of Rang et al. (Applicant cited reference: Rang et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Duke University, 2000) and further in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Broder et al. teaches a method of treatment of bronchorestriction in a human or animal, comprising administering an effective amount of a drug selected from the group consisting of D-propranolol (claims 1-3, abstract). The reference teaches administration of 10 mg/kg dosage (A 25 kg patient will be administered an amount of 250 mg) of D-propranolol in a method of treatment of asthma, a pulmonary disorder (col. 12, lines 16-18). The reference does not explicitly teach that modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Broder et al. teaches administration of propranolol 250 mg/day (to a 25 kg patient). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Broder et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to same subjects with abnormality in autonomic nervous system as claimed in the dosage amount recommended in the specification of the instant application.

The reference does not teach that the method further comprises of determining the sympathetic and parasympathetic functions are substantially equal.

Rang as cited by Applicants' in the specification teaches non invasive procedure to assess the autonomic cardiovascular control in patients with hypertensive disorder (See abstract).

Autonomic dysfunction document teaches various methods to measure the autonomic functions by analyzing heart rate, blood pressure variability etc.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the equality in sympathetic and parasympathetic functions by using the methods taught by Rang and Autonomic dysfunction document. One having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal because evaluation or assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation etc.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the

time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals.

Response to Arguments

(1) 112(1) Written description rejection:

Applicants' argue that the specification provide adequate description for methods of administering beta blockers in a subject (example p 14, line 14 to p25 line 4). In response, Applicants' describe the "embodiments of the subject method include administering…(p 14), depending on the particular beta-blocker(s) administered to a subject, the beta-blocker(s) may be administered to-a subject using any convenient means.. (para 0045), the beta blockers may be administered orally, intranasally (para

47-51), pharmaceutical carriers, routes of administration etc are discussed (p 14-25). In summary, the specification in general teaches the dosage administration, routes, types of delivery, examples of beta blockers and non-beta blockers. However, the specification does not provide data or show any examples of actual administration of beta blockers in conditions arising from modulation of autonomic nervous system. Also, there is no specific data or examples providing administration of a non-beta blocker along with a beta blocker. The scope of claim 1 is to use any beta blocker in patients with one more conditions arising from modulation of autonomic nervous system. The conditions claimed in claim is a laundry list of conditions (wide variety of unrelated conditions) that includes several classes which can be further divided into sub classes. The subject can be human or an animal. Accordingly, the conditions for formulation, dosages and administration need to be different. For example, neurodegenerative conditions include an array of conditions including Alzheimer's, Huntington's disease, cerebral palsy, spinal muscular atropy etc. Applicants' have propranolol as the beta blocker, elected aging associated condition as the species in general and loss of parasympathetic function as sub species. However, the species elected "aging associated conditions" include a variety of disorders cancer, heart disease, hypertension, shy dragers, multi-system atrophy, inflammatory conditions etc. As such cancer disease can be classified into a variety of subtypes including breast, colon, kidney, testicular cancer, ovarian cancer etc to name a few. The specification does not give any specific guidance to age associated conditions resulting from modulation of autonomic nervous system regarding (1) criteria for the dosages for specific age

associated conditions (2) criteria for the counter indications in giving such beta blockers (3) criteria of dosage regimens for specific conditions e.g. when the dose needs to be administered, how many doses etc (4) criteria if patients suffer from multiple associated conditions. The Wikipedia document on propranolol (http://en.wikipedia.org/wiki/ Propranolol) states that propranolol, a non-selective beta blocker is used in treating hypertension. The reference teaches the indications of the drug and also indicates that beta blockers are downgraded to fourth line drugs for treating hypertension as they perform less well than other drugs, particularly in the elderly, and evidence is increasing that the most frequently used beta-blockers at usual doses carry an unacceptable risk of provoking type 2 diabetes. The reference further lists the contraindications of the drug for patients with certain disease conditions and the drug interactions with other drugs including “non-steroidal anti-inflammatory drugs”. As cited in the reference the drug dosage varies with conditions, e.g. hypertension (120-130 mg), tachyarrhythmia (10-40 mg). The beta blockers are classified into alpha1 (selective), alpha 2 (selective), non selective (beta , alpha), beta 1 selective, beta 2 selective, beta 3 selective. There are at least twelve non selective beta blockers (Alprenolol, Amosulalol, Bupranolol, Metipranolol, Nadolol, Oxprenolol, Penbutolol, Propranolol, Tertatolol, Timolol, Tilisolol, Sotalol) known. Age related conditions include circulatory conditions (coronary heart disease, stroke), Respiratory diseases, cancer, neurological and cognitive conditions (dementia, Alzheimer’s, Parkinson’s), sight and hearing and muscular and skeletal degradation. The symptoms and disease conditions of patients with such conditions worsen with age and also if not treated. The patients can have multiple disease

conditions and the therapy has to be patient specific and the conditions need to be monitored and it is not a trivial matter. Accordingly, the scope of the claims are broad. Also, the method claims comprise administering a non-beta blocker (claims 23 and 24) and applicants' have selected non-steroidal anti-inflammatory (NSAID) drug as the species. According to Wikipedia document (http://en.wikipedia.org/wiki/Non-steroidal_anti-inflammatory_drug) the drugs include COX-2 inhibitors, sulphonanilides and other drugs. The reference teaches the adverse effects of the NSAIDS, gastrointestinal and renal effects of the agents. The reference states in combinatorial risk that patients on daily aspirin therapy (as for reducing cardiovascular risk or colon cancer risk) need to be careful if they also use other NSAIDs, as the latter may block the cardioprotective effects of aspirin. Also, the reference states that “A recent meta-analysis of all trials comparing NSAIDs found an 80% increase in the risk of myocardial infarction with both newer COX-2 antagonists and high dose traditional anti-inflammatories compared with placebo. (Kearney et al., BMJ 2006;332:1302–1308) and NSAIDs aside from aspirin are associated with a doubled risk of symptomatic heart failure in patients without a history of cardiac disease. In patients with such a history, however, use of NSAIDs (aside from low-dose aspirin) was associated with more than 10-fold increase in heart failure. If this link is found to be causal, NSAIDs are estimated to be responsible for up to 20 percent of hospital admissions for congestive heart failure. Accordingly, precautions need to be taken in administering an NSAID along with a beta blocker for patients with cardiovascular indications. The specification has not given any guidance (1) in regards with counter indications of all the NSAIDs claimed (2)

the dosage amount to be provided with respect to age related conditions to make sure there are no adverse effects or the side effects are to a minimal (3) precautions in administration of drugs for patients with more than one condition. The claims are directed to a method of treating conditions arising from modulating the autonomic nervous system. The number of conditions listed in claim 1 are 30, the limited number of beta blockers claimed (claim 21) are 16, number of non-beta blocker agents claimed are 39 and hence the combinations totals 30X16X39 for the conditions listed. This does not include the subclasses of the conditions, subclasses of beta blockers, sub classes of non-beta blockers. As such it is not predictable from the art which combination of beta blockers and non-steroidal inflammatory drugs would be safe in combination therapy and also what dosage needs to be given for patients with specific condition(s). There is no specific guidance (with respect to dosage regimens, drug interactions, contraindications etc) to provide treatment for older patients in the specification and there is no disclosure of administration of a combination of a beta blocker with a non-beta blocker even for one of the disease condition(s) claimed. Accordingly, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(2) 112(1) Scope of Enablement

Applicants' argue that the present application does provide sufficient disclosure to enable the invention to the full scope of the pending claims and further argue that the claims are not broad as the conditions associated all contain common element of being

caused by an abnormality in autonomic nervous system. In response, Applicants' in general provide the dosage administration, routes, types of delivery, examples of beta blockers and non-beta blockers and describe the conditions arise from modulating the autonomic nervous system. However, as stated above, the scope of the claims is very broad with respect to the beta blockers (alpha1 (selective), alpha 2 (selective), non selective (beta , alpha), beta 1 selective, beta 2 selective, beta 3 selective), and the number of beta blocker drugs known and yet to be discovered, the number of conditions associated with the autonomic nervous system dysfunction, and all the non-beta blocker drugs to be co-administered along with the beta blockers. The conditions associated have a common element or mechanism but however each condition is distinct and some classes of conditions are unrelated (e.g neurodegenerative conditions and renal failure). Though they have a common link each disorder requires guidance in treatment of specific disease condition especially when treating old age patients. Also, patients with multiple conditions requires a different form of treatment with respect to formulation, dosage regimen. The treatment of any disease in general depends on a number of factors that includes age, health status, co-administration of other drugs etc. The specification does not provide any specific guidance with respect to treating elected aging associated conditions in regards to the dosage regimens, specific disease conditions in older patients. The specification does not provide any in vitro or in vivo data pertaining to administration of any beta blocker(s) and a non-beta blocking agent in any of the conditions modulating the autonomic nervous system. The specification fails to provide guidance with respect to the contraindications of the beta blockers and drug

interactions of such agents with non beta blocking agents. As stated above, the prior art teaches that evidence is increasing that the most frequently used beta-blockers at usual doses carry an unacceptable risk of provoking type 2 diabetes. The Wikipedia reference further lists the contraindications of the drug, propranolol for patients with certain disease conditions and the drug interactions with other drugs including “non-steroidal anti-inflammatory drugs”. As cited in the reference the drug dosage varies with conditions, e.g. hypertension (120-130 mg), tachyarrhythmia (10-40 mg). This is just with one non-selective beta blocker propranolol. However, claim is directed to all beta blockers available and yet to be discovered. The number of conditions listed in claim 1 are 30, the limited number of beta blockers claimed (claim 21) are 16, number of non-beta blocker agents claimed are 39 and hence the combinations totals 30X16X39 for the conditions listed. This does not include all the sub classes of the beta blockers or all the sub classes of a laundry list of non-beta blockers (claims 23, 24). With Applicants’ guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct these experiments administering beta blockers for the conditions listed in claim 1 and with combination of non-beta blockers listed in claim 24. Considering the unpredictability of the combination of compounds due to the drug interactions and contra indications, this would be an arduous and daunting task to treat a condition caused by an abnormality of autonomic nervous system comprising administering a beta blocker with a non beta blocker agent. It would require undue experimentation to test each beta blocker for all the conditions listed in a method of modulating the autonomic nervous system and treating the subjects for those

conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. It would require undue experimentation to test each beta blocker with every single non beta blocking agent listed in claim 24 for every condition listed in a method of modulating the autonomic nervous system and treating the subjects for those conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. It would require undue experimentation to test all beta blockers for every condition listed in a method of modulating the autonomic nervous system and treating the subjects for those conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta-blocker to said subject to treat said subject for at least one of the conditions listed in claim 1.

Applicants' argue that from Stocky's teachings of two patients with adverse reaction, which can occur with any medication or treatment. In response, it is recognized that adverse or side effects can occur with any medication. However, with no specific guidance to one of ordinary skill in the art to which combination of (beta blocker and non-beta blocker) to use for treating the conditions claimed it would be a

daunting task to one of ordinary skill in the art to predict the combinations to practice the claimed invention. There is no clear guidance to age associated conditions with respect to dosage regimens, contra indications of the drugs or drug interactions as such and also the actual practice to reduction is not shown. Without specific guidance (such as dose selection, patient specific, disease specific etc) in the specification or in the prior art it would be an undue experimentation for a person of ordinary skill in the art at the time of the invention to administer a beta blocker with a non beta blocker in treating conditions associated with autonomic nervous system dysfunctions especially for aging associated conditions (elected) in elderly patients. In general, the dose selection of any drug in elderly patients should be done cautiously. Also, precautions must be taken with respect to the type of delivery, formulation and the co-administration of other drugs (with respect to drug interactions). Accordingly, it would be an undue experimentation to one of ordinary skill in the art to practice the claimed invention.

(*3) 103(a) rejections*

(a) Lampert et al. (b) Guilli et al.in view of Bugiardini et al. (c) Hill in view of Lampert et al. (d) Garrett et al.

Applicants' argue that the Examiner has not pointed to where the reference teaches or suggests that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Furthermore, nowhere in the reference is the teaching or suggestion of determining that the parasympathetic and sympathetic functions are substantially equal, as in the current claims.

(a) Lampert et al.

Lampert et al. teach that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients. Hence by administration of the drug claimed namely, propranolol to patients in the recommended dosage would obviously have the same pharmacological effects in modulating the sympathetic and parasympathetic activities. The modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed, because Lampert teach the same compound with the dosage amount recommended in the specification of the instant application.

(b) Guilli et al. in view of Bugiardini et al.

Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity and Bugiardini et al. teach administration of propranolol to patients with X syndrome. Hence by administration of the drug claimed namely, propranolol to patients in the recommended dosage would obviously have the same pharmacological effects in modulating the sympathetic and parasympathetic activities. The modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed,

because Bugiardini et al. teach the same compound with the dosage amount recommended in the specification of the instant application.

(c) Hill in view of Lampert et al.

Hill et al. teach beta-blockers such as propranolol in a medical procedure such as beating heart surgery, arrythmias, vascular surgery, neurosurgery etc which are aging associated conditions. Lampert et al. teach that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients. Hence by administration of the drug claimed namely, propranolol to patients in the recommended dosage would obviously have the same pharmacological effects in modulating the sympathetic and parasympathetic activities. The modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed, because Lampert teach the same compound with the dosage amount recommended in the specification of the instant application.

(d) Garrett et al.

Garrett et al. teach administration of a beta blocker such as propranolol 1mg/kg to modulate autonomic nervous system in salivary glands and further teaches that parasympathetic and sympathetic systems can be stimulated by administration of a beta blocker such as propranolol. Hence by administration of the drug claimed namely, propranolol to patients in the recommended dosage would obviously have the same pharmacological effects in modulating the sympathetic and parasympathetic activities.

The modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed, because Lampert teach the same compound with the dosage amount recommended in the specification of the instant application.

Conclusion

No claims are allowed.

Applicants' amendments necessitated the new and modified rejections presented in this office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone

number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617